A REVIEW OF THE SECONDARY ANEMIAS

PART II*

By O. H. PERRY PEPPER, M. D.
Philadelphia, Pennsylvania

TRUE SECONDARY ANEMIA

We are now ready to discuss true secondary anemia—by which term let us understand ourselves clearly. We now mean anemia due to a definite, recognizable cause, no matter how difficult the discovery of that cause may be. The presence of a secondary anemia is a challenge to our diagnostic skill. Secondary anemia is not a disease, it is only a symptom; it must have a cause and this cause we must discover. There is danger in a too ready acceptance of the conception of frequently occurring idiopathic secondary anemia.

Idiopathic secondary anemia is an old concept, but it is receiving renewed emphasis today and in a manner with which I have little sympathy.

In a classification of secondary anemia issuing recently from one of the leading clinics of this country, all chronic secondary anemia is divided into three groups—a type due to hemorrhage, a type due to some organic lesion, and a type termed "idiopathic secondary anemia." The first two types need no comment, but chronic idiopathic secondary anemia is then subdivided into five types on the basis of the blood morphology.

These five subtypes are each to be recognized and employed as the indication for varying forms of treatment. This is going ahead of our established knowledge. We need such researches and we will be most grateful to him who establishes such new data, but until it is proved and simplified it is beyond our routine use.

Face to face with a patient with unexplained anemia, it seems to me our mental process is somewhat as follows: Is this one of the specifically recognized forms of anemia—pernicious anemia, hemolytic ictero-anemia, sickle cell anemia, for example? Is it a case of secondary anemia and if so from what cause? Only after most exhaustive study would it ever occur to me to be tempted to make a diagnosis of chronic idiopathic secondary anemia—rather would I doubt myself and the adequacy of my search for the underlying undiscovered cause. Nor would I be amazed that my treatment of such patients was not more successful—how could I anticipate cure when I had failed to recognize the cause? For practical purposes a patient with secondary anemia is never idiopathically anemic.

The causes of secondary anemia are legion: hemorrhage, acute and chronic; infections; neoplasms; parasites; chemicals; irradiation; dietetic deficiencies, for example. Rather than discuss each in detail let me describe the blood findings of secondary anemia and then select for fuller discussion a few of the causes which are of special practical interest.

Secondary anemia may be of any grade of severity from the mild degree so commonly encountered as almost to persuade us to accept it as physiologic to the most intense and life-threatening anemia. Severity of anemia is no proof, in fact not even an argument in favor of its primary or pernicious nature.

Characteristically, a secondary anemia exhibits a reduction of the hemoglobin content of the red cells—in other words, the color index is low or at least is below one, or to be even more guarded in our statements, the color index is not above one. In terms of red cell count and hemoglobin percentage, this means that the hemoglobin is reduced more than the red cell count. The extreme example of this is seen in chlorosis, and those instances of secondary anemia which exhibit this relationship, to a marked degree, are termed chlorotic anemia.

At the other end of the scale are those instances of slowly developing secondary anemia which most closely simulate pernicious anemia. These have a color index approaching or equal to one, but not above. They do not, however, present any increase in the size of the red cells and to my mind they are clearly secondary anemias no matter how much they may approach primary anemia in some respects. This group includes especially the instances of anemia from certain growths of the colon and from certain parasites.

The further hematology of secondary anemia adds little to the information given by the blood count. Usually the red cells are of subnormal size and of normal resistance to hypotonic salt solution. The white cell count varies according to the underlying condition and the acuteness of the anemia. Similarly the percentage of young red cells varies with the activity of the bone marrow's response to the anemia, high after an acute hemorrhage, low in the late stages of a long-drawn anemia approaching an aplastic picture.

CLINICAL TYPES OF SECONDARY ANEMIA

Acute Hemorrhage.—Of the many important forms of secondary anemia, let us first mention that following acute hemorrhage. We must remember that reduction of the blood volume is in one sense anemia—but not in the usual sense. Anemia in its clinical sense does not appear instantly after an acute hemorrhage, in fact hours must elapse before the passage of fluid into the blood from tissues and gastro-intestinal tract restores the blood volume to normal and by dilution lowers the number of red cells per unit of blood. Thus anemia results.

The body has reserves of blood cells in spleen and bone marrow ready for emergency calls and a considerable acute loss of blood is required to cause any distinct degree of anemia. The blood loss at most surgical operations is far below the amount required to bring about anemia. When a patient is found to be severely anemic promptly after what seems to be a single acute hemorrhage, one is quite safe in assuming that anemia was present before. This is the case very often

* Editor's Note.—Part I of this contribution appeared in the April issue of California and Western Medicine, page 233.

with patients with duodenal ulcer. A sudden hemorrhage may seem to lower their hemoglobin to 40 per cent, their red cells to 3,000,000; but in actual fact the ulcer had been bleeding insidiously for weeks before the acute hemorrhage and the blood count before the severe hemorrhage was probably 60 per cent of hemoglobin and 4,000,000 red cells. The more acute the hemorrhage the more marked is the general bone marrow response, and the more evidence of bone marrow activity appears in the circulating blood.

Obscured Anemia.—Just as dilution of the blood must occur after acute hemorrhage before anemia is demonstrable by blood count, so dehydration of the patient may wholly hide a fairly severe degree of secondary anemia. This is seen, perhaps, most markedly in cases of pyloric obstruction. The patient is sent to the hospital for operation—he is dehydrated from loss of fluid incident to the pyloric closure. The blood count reveals a normal or even mildly polycythemic picture. In preparation for operation large amounts of fluid are supplied by vein and bowel—the patient improves greatly; his weight rises, but a second blood count reveals a far lower level than on admission. This fall may be misinterpreted as being due to hemorrhage; or to the progress of malignancy; its true explanation is the relief of the dehydration. The higher figures of the first count were for that patient a sort of physiologic polycythemia. It is always well to remember this possibility and repeat the blood count after preoperative preparation; it may reveal such a state of anemia as to make it advisable to give a preoperative transfusion.

This same obscuring of anemia by dehydration is a common observation in severe infection with high fever. Only after the fever breaks does the patient look pale and washed out and the blood count reveal the true level of anemia.

Secondary Anemia From Chronic Hemorrhage. There is no more familiar fact than that severe anemia may result from long-continued or oft-repeated slight bleeding, but it is a little hard to keep in mind how very severe the anemia may be, and from how very inconspicuous a loss of blood the anemia may arise. It is like the dropping water which in time wears away the stone.

Hemorrhoidal bleeding supplies many instances of this as, for example, the following case: W. B. (Med. Clin. U. of P. H. 1928, A. B. 548), a male, thirty-two years of age, was admitted with the history that he had had bleeding from the rectum for seven months. He was first told he had "bleeding piles," but later a suspicion of cancer of the rectum arose as a result of loss of weight, severe anemia, and a roentgenologic study with barium enema. On admission, the blood count was: hemoglobin, 20 per cent; red blood cells, 2,620,000; white blood cells, 6000; marked changes in morphology of red blood cells; differential white count, normal; reticulated cells, three per cent.

No neoplasm was found, but bleeding from hemorrhoids was demonstrated; hemorrhoidectomy performed followed by a prompt rise in the count to 40 per cent of hemoglobin and 3,350,000 red blood cells. This degree of improvement in the blood level rid the patient of all the complaints arising from the anemia.

This is but one case of many which I might quote and which most of you can duplicate from your own experience. Often the bleeding of hemorrhoids is not recognized by the patient and may not be seen on rectal or proctoscopic examination. In unexplained secondary anemia the clinician should be stubborn in abandoning his suspicion of this cause.

Hemorrhage from gastric polyp is also a most important and interesting cause of profound anemia. My first experience with it was a tragic one. In 1918, while on duty at the Base Hospital at Camp Meade a soldier was admitted to the medical service of Major Nellis B. Foster. The young man was intensely anemic without any cause which we could discover with the somewhat inadequate means at our disposal. After our best efforts at diagnosis we unwillingly termed the case one of pernicious anemia, gave five transfusions and discharged the patient very much improved and with normal or almost normal blood picture.

Eighteen months later, after the war, he came to me at the University Hospital and was found to have a gastric polyp which had undergone malignant change. In retrospect, there is not much doubt but that his original anemia had been due to bleeding from this polyp which at that time was probably nonmalignant and could have been easily and permanently removed. As it was, there were metastatic lesions and the patient survived the operation only three weeks.[5 6]

Hemorrhage is a common occurrence not only from malignant, but also from benign gastric polyps. As Miller[5 6] of our clinic recently wrote, "If a bleeding gastric polyp is not considered in every case of obscure anemia, certain cases will be entirely misdiagnosed."

Carcinoma of Colon.—The same remark might with almost equal truth be made of cancer of the colon. Here slow bleeding, malignancy and sometimes disturbed nutrition are present, and it is difficult to evaluate the importance of these several factors as possible causes of the anemia. When the anemia is intense and blood is found in the stools, it is often difficult to say whether the anemia is the result of the bleeding or the bleeding a result of the anemia. Unfortunately, in extreme anemia oozing may occur from various mucous membranes and both aggravate the anemia and confuse the diagnosis.

Cancer of the colon is, perhaps, that cause of severe secondary anemia which produces a blood picture most closely approaching that of primary anemia. This must be constantly kept in mind to avoid diagnostic errors.

Secondary Anemia in Infections.—Among the infections which have a special tendency to cause a severe secondary anemia are: acute rheumatic

fever, streptococcus viridans endocarditis, malaria, syphilis and spirilla diseases in general.

All infections of long duration, such as typhoid fever and tuberculosis, are accompanied by anemia. Personally I have very seldom seen tuberculosis masquerade as an anemia although this is frequently reported. In syphilis, severe anemia is more often the result of treatment than of the disease.

In this connection it is well to remember that most patients seriously anemic from any cause will exhibit some degree of fever. This must not be used as an argument to favor an infectious cause for the fever, as is often done. For example, let the blood be restored to normal by liver therapy in pernicious anemia or other means and the fever will disappear.

Chemical poisons may cause severe secondary anemia of varying types: potassium chlorate, rapidly by blood destruction; lead more slowly, probably by action on the erythrocytes, and benzol by a damaging action on bone marrow function. These are but examples of a multitude of chemicals to which we are daily exposed—in foods, in the city air some must breathe, in many unsuspected contacts. It is hard to believe that we know all about this topic in view of the rapidly developing science of industrial chemistry. We must be on the alert.

Cases come to mind to support this view. Some years ago an unexplained patient with anemia stayed for weeks in our women's ward. Improvement seemed to follow the clearing up of oral sepsis, but it was not until it was discovered that right under our very eyes the patient was daily using white lead as a face powder, was the true nature of her anemia discovered. Similarly hair dyes may cause anemia from their content of lead.

Another patient, a man, had an obviously aplastic anemia; no explanation was forthcoming. He was questioned as to his work; he was a salesman "on the road" with some line, innocuous at least to the seller. It was not until some days later that a chance remark led to the information that he had purchased an interest in a rubber goods factory and had been doing a little experimenting with benzol and other solvents. Death occurred in spite of our best efforts.

There are literally scores of other causes of secondary anemia which might be mentioned. We have had referred to the medical clinic at the University Hospital cases of malaria, of chronic nephritis, streptococcus endocarditis, all with the referring physician's diagnosis of primary pernicious anemia. We have had an advanced thinker admitted in such a state of anemia that it was not until after transfusion that we were able to elicit his story of such a strict vegetarianism that he would not take a capsule for fear that it was made of gelatin from a horse's hoof. Doctor Kern of our clinic will shortly put this remarkable case of dietetic anemia on record.

Nothing is to be gained by following this thought further. What I have said is perhaps familiar and trite, but those of us who deal with the patient know how often we fail to get to the bottom of a case of secondary anemia. Just before I left the East I looked over again a group of records in our record room on which the diagnosis of "secondary anemia" is given as the primary diagnosis. A study of these records leads to a sense of inadequacy and humility in me rather than to a desire to label them idiopathic and let it go at that.

TREATMENT OF SECONDARY ANEMIA

First, search for the cause; second, keep on searching; third, look for secondary coöperating causes; fourth, treat the cause. During this time it may be necessary and advisable to treat the anemia, but do not let the doing of this take one's mind off the search for the original cause.

The following case history will point this moral: A woman in her forties, the wife of a college professor, spent the four fall months of 1929 in, perhaps, the leading mental sanitarium of the East. There was no mental disease, but extreme nervousness and despondency owing to unhappy home conditions.

On October 24 at the sanitarium the blood count was: hemoglobin, 62; red blood cells, 3,750,000. This anemia was casually attributed to bleeding hemorrhoids, for blood had been observed on the stools for several months. She had also become increasingly constipated and had been losing weight and strength. It was not until the middle of January 1930 that the psychologists noticed her increasing pallor; the hemoglobin was found to be 45 per cent, and she was hastily returned to Philadelphia. On admission to our hospital the hemoglobin was 36 per cent and the red blood cells 3,000,000.

A rectal examination revealed an enormous ulcerating carcinoma. After several transfusions the growth was successfully removed by radical surgery and today the patient is in excellent health with a normal blood count and but little disturbed by her colostomy, which is quite well behaved.

This brief history is most significant and could be made the text for many remarks on the need of thoroughness, the danger of overspecialization, et cetera.

Transfusion.—When the anemia is very severe, it may be wise to transfuse at once. This will protect the patient for the moment from the immediate dangers of severe anemia and will give time for further search for the cause of the anemia. By raising the blood level one can often also put an end to the mucous membrane's oozing which may confuse the recognition of the primary cause. Furthermore, one or more transfusions will often be necessary to put the patient into condition to undergo treatment for whatever primary cause is discovered.

I firmly believe that transfusions are not resorted to freely enough in cases of moderate secondary anemia, but are used far too freely and uselessly in hopeless cases of incurable dis-

ease. The prolongation of a suffering life is not a very desirable indication for transfusion. In secondary anemia, however, they are of inestimable value and the danger of reaction is far less in secondary anemia than in a primary blood disease.

In secondary anemia from infection a transfusion is very valuable not only to help combat the infection, but in cases where the infection is at an end and the patient faced by a long, slow recovery the convalescence may often be much shortened by a transfusion.

Certain treatments of disease cause a secondary anemia or an increase of the anemia due to the disease itself. Thus in leucemia of the myelocytic type, it is often anemia which forces a cessation of x-ray or radium treatment, and severe anemia is not uncommon in the lead and radium treatment of inoperable cancer. In such cases transfusion is clearly indicated.

In secondary anemia, then, transfusion should be employed for a variety of indications and without waiting for an alarming degree of anemia to develop. I have only one possible complaint about transfusion in chronic unexplained secondary anemia, which is, that occasionally following transfusion the anemia for the time being remains relieved and one neglects to search for the cause. In primary anemia, transfusion may be needed to tide the patient over until the specific maturation stimulants have time to act.

Iron.—The modern investigations confirm the long-established clinical belief in the value of iron in the treatment of anemia. Also the modern view agrees with older, that it is in chlorosis and in the secondary anemias most closely resembling chlorosis that iron is most efficacious.

It is an interesting corollary on our reactions to scientific advances that when it was appreciated what a small amount of iron was present in the total blood the doses of iron given therapeutically became smaller and smaller. Only recently have we returned to larger doses and the results have been far better. It may seem illogical to deal in quantities of iron many times in excess of what would seem to be the body's maximum needs, but the results justify the procedure. Possibly iron acts also through the so-called "salt action" and only when supplied in larger amounts.

In those secondary anemias which are benefited by liver in one form or another, iron in large doses enhances the liver action. The literature contains many reports to indicate that treatment with liver and iron is more effective than the use of either alone.

Concerning the importance of copper as an adjuvant to iron treatment, the evidence is far from satisfactory.

Only the empiric evidence of the past supports the use of arsenic in anemia.

When iron is indicated, give it in a simple form, such as reduced iron, and give it in large doses. Schulten [7] reports good results from six grams of reduced iron daily, given in thirty three-grain pills each day. Smaller doses gave no such benefit, while one patient improved only when the dose was increased to nine grams a day.

Diet.—There is no doubt concerning the accuracy and the fundamental importance of the studies—many of the most brilliant having been done in California—of the influence of diet on blood regeneration. These studies, which led directly to the modern liver treatment of pernicious anemia, must not be lost sight of.

Nor is there any doubt that severe anemia will result from grossly abnormal and deficient diets. The case already quoted is an example of this, and Minot and others have reported similar observations.

It is in such instances of anemia due to faulty diet that a change to an adequate well-chosen diet is of the greatest value. No doubt a diet rich in green vegetables, fruit, and red meat is a desirable adjunct to the treatment of any form of anemia, but alone it is curative only in truly nutritional and chlorotic anemias. Even in these one must often add iron, and perhaps liver as well to obtain rapid improvement. When the diet has been grossly abnormal, one is really treating the cause of the anemia in restoring the patient to a satisfactory regimen. As a rule, however, the wide margin of safety in the diet of this country makes it unlikely that an anemia has a strictly nutritional basis. Furthermore, in many cases it will prove easier to supply iron directly than to disturb a patient's fairly reasonable dietary by forcing foods supposed to be rich in iron. There is no good evidence that the iron of food is any more useful than iron administered directly, nor that organic iron is better than inorganic, nor that there is any choice between the ferrous and ferric salts.

Probably the vitamins have little usefulness in the treatment of any anemia unless the diet has been markedly deficient along this line.

With regard to the use of liver in the treatment of secondary anemias in general, it may be said that the evidence is rapidly accumulating to prove that the various extracts so valuable in the treatment of pernicious anemia are of relatively little value. Whole liver is far more effective in secondary anemia and should be employed in large amounts and in conjunction with iron. The newer liver extracts for use in secondary anemia have great promise, but have not yet proved their practical value.

Specific Erythropoietic Stimulants.—It is interesting to recall that all of the liver therapy of pernicious anemia grew out of studies of the effect of various foods upon experimentally produced secondary anemia. From this beginning we have seen the progression from whole liver to a great variety of liver extracts, fetal liver, hog's stomach, ventriculin, and extracts of bone marrow and spleen. We know the startling efficacy of various of these in pernicious anemia, but we are still far from sure about their action in secondary anemia. Which are helpful and in which form of secondary anemia? On the whole,

the results have been disappointing. Whole liver has been most efficacious, but perhaps the answer has been found in the isolation of a new fraction of liver potent in certain secondary anemias, although not so in pernicious anemia.

On a theoretical basis one might assume that those instances of secondary anemia whose blood picture most closely resembled pernicious anemia would be most benefited by the extracts potent in pernicious anemia. This is not the case, but it is true that benefit is most often obtained with these extracts in those instances of apparent secondary anemia which, through lack of recognized cause, one must term cryptogenic or idiopathic.

In an article about a year ago, Murphy [8] of Boston expressed amazement at the dearth of accurate information to determine the most effective treatment of the so-called secondary anemias from various causes. He then outlined the treatment for six different types of secondary anemia. This is the crux of our difficulties: secondary anemia is not a single disease, it is a symptom of many diseases, a condition brought about by many causes. There never will be one effective therapy for all secondary anemia. Should an extract be obtained which proved to be effective in stimulating blood formation in chronic secondary anemia, it would often fail unless the cause of the anemia was discovered and treated. In fact such an extract would do harm in that by its available efficacy it would lead to a less insistent search for the etiology of the anemia. In the final analysis the only true treatment of a symptom is the treatment of the causative condition.

CONCLUSIONS

We must bring this review to an end even if we have but inadequately covered the important subject of secondary anemia.

1. Secondary anemia is only a symptom, but it handicaps the sick, delays convalescence, and takes the zest of life out of many supposedly healthy persons.

2. Before making the diagnosis of secondary anemia, one should be sure to rule out the various other special forms of anemia.

3. The diagnosis—secondary anemia—implies a cause. Every effort to discover this cause must be made.

4. To treat secondary anemia and neglect the cause is stupid and criminal.

5. To treat the cause and neglect a severe secondary anemia is to increase the risk of wasting your efforts and the patient's time.

6. Severe secondary anemia is the strongest indication for blood transfusion.

7. Both cause and anemia should be treated in even the mildest case.

8. Diet alone should be expected to cure anemia only when the previous diet has been grossly abnormal.

9. When iron is to be administered, use a simple form but in large doses.

10. Do not employ the preparations intended for the treatment of pernicious anemia in secondary anemia. Use either whole liver or a preparation intended for use in secondary anemia.

11. Do not expect one form of treatment to act in all forms of secondary anemia.

550 Maloney Pavilion, University of Pennsylvania Hospital.

REFERENCES

5-6. Case reported by Miller, T. G. J. Am. Med. Assn., 76, 229, 1921, and included in Miller, T. G., et al. Arch. Int. Med., 46, 841, 1930.

7. Münch med. Wchnschr., 77, 355, 1930.

8. Surg. Gyn. and Obst., 50, 246, 1930.

ENDOMETRIOSIS*

By ALICE F. MAXWELL, M. D.
San Francisco

DISCUSSION *by Robert Glenn Craig, M. D., San Francisco; John C. Irwin, M. D., Los Angeles.*

GYNECOLOGIC literature of recent years contains no finer example of scientific research than is presented by the histologicoclinical studies upon the subject of ectopic endometrial tissue. Despite the general interest in the matter, so far the question of origin of this tissue has not been settled nor has terminology been determined. The frequency, wide distribution, variation and severity of symptoms demand identification and proper treatment of these lesions.

ORIGIN OF ENDOMETRIOSIS

Endometriosis, endometrioma, endometrial adenoma, müllerianoma, chocolate cysts, hemorrhagic perforating cysts of the ovary, Sampson's tumors and adenomyoma are a few of the synonymous terms applied to tissue resembling uterine mucosa histologically and functionally which is found elsewhere than in the uterine cavity. Although early writers (von Rokitansky, von Recklinghausen, Russell and Pick) had described tissues in the ovary and uterine musculature which were an exact prototype of uterine glands and stroma, Cullen, in his publications on adenomyoma of the uterus (1896) laid the foundation of our knowledge of endometriosis when he demonstrated that these tumors were invasive growths of the uterine mucosa. Following the appearance of Sampson's monumental work in 1922, new interest in the subject was stimulated which has furnished many interesting facts.

THEORIES OF ORIGIN

Von Recklinghausen ascribed the origin of the glandular elements of adenomyoma to embryonic rests of the Wolfian body or Müllerian duct.

Sampson has advanced the theory that pelvic endometriosis develops, not from embryonic rests, but from bits of endometrium or tubal epithelium which have escaped from the uterus or tubes during menstruation as a back spill and

* Read before the Obstetrics and Gynecology Section of the California Medical Association at the fifty-ninth annual session at Del Monte, April 28 to May 1, 1930.